REMARKS

Reconsideration of this application is respectfully requested. Claims 1, 18-22, 24-26, and 28 have been amended. Claims 23 and 31 have been cancelled. New claims 35-39 have been added. With these amendments, claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, and 32-39 are currently pending in this application. These amendments are made without prejudice or disclaimer and do not add any new matter. Applicants retain the right to prosecute any cancelled or otherwise unclaimed subject matter in a continuing, divisional or other application as appropriate. Consideration and entry of this reply is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 11, 12 and 18-23 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. These rejections are addressed below.

(i) Claims 18-22 stand rejected under 35 U.S.C. § 112, second paragraph because of the reference to IFNα2b being administered in step (a). These claims have been amended to indicate IFNα2b is administered in step (b). This portion of the rejection is therefore moot.

Claims 18-22 also stand rejected under 35 U.S.C. § 112, second paragraph, as to the term "at least 10 MU/m^2/day", the question being whether "/day" refers to administration on a daily basis (e.g., every day). The term is meant to indicate, for instance, that step (b) begins on day 1 with administration of at least 10 MU/m^2 IFNα2b through the course of that day, which may then be repeated at a particular interval, such as every day (e.g., daily), a certain number of times per week (e.g., three times per week), or the like, as desired. Thus, term "/day" refers to the amount that is administered during the course of one day (e.g., "per day"). Applicants believe the meaning of this term would be understood by one of skill in the art and therefore request that these rejections be withdrawn.

(ii) Claim 23 stands rejected under 35 U.S.C. § 112, second paragraph as to the term "modified gp100". Claim 23 has been cancelled; this rejection is therefore moot.

(iii) Claims 11 and 12 stand rejected under 35 U.S.C. § 112, second paragraph as to the listed tumor antigens. The Examiner alleged that "the specification and the status of the art do not support that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen" are melanoma-associated antigens. Applicants respectfully disagree.

It is first pointed out that to be "melanoma-associated", Applicants do not mean that a particular antigen cannot be expressed anywhere else in the body. As described in Applicants' specification (e.g., paragraphs [0015]-[0017], tumor antigens ("TA") may be "tumor-associated" (e.g., TAA) or "tumor-specific" (e.g., "TSA"). Only a TSA is described as being "unique to tumor cells and [] not expressed on normal cells" (paragraph [0017]). Thus, the Examiner's argument that the claim is indefinite because none of NY-ESO-1, BAGE, or GAGE are "tumor specific" is inconsistent with both the Applicants' use of the term and what Applicants believe would be the skilled artisan's understanding thereof.

Furthermore, in describing NY-ESO-1 at paragraph [0018], Applicants' specification points to WO 98/14464 (pub. April 9, 1998, which corresponds to U.S. Pat. No. 5,804,381). As shown therein, NY-ESO-1 is expressed in melanoma tumor tissues (e.g., Table 4). Thus, both the specification and the art support the position that NY-ESO-1 is a melanoma-associated antigen.

In describing BAGE at paragraph [0018], Applicants' specification points to Boel, et al. (Immunity, vol. 2, pp. 167-175, pub. Feb. 1995; attached). As shown therein, expression of BAGE was observed in melanoma tumor tissues (e.g., p. 169, first column, second full paragraph, BAGE "is expressed mainly in melanomas (22%)", see also Table 2). Thus, both the specification and the art support the position that BAGE is a melanoma-associated antigen.

In describing GAGE at paragraph [0018], Applicants' specification points to Van den Eynde, et al. (J. Exp. Med., 182: 689-698 (1995), attached) and U.S. Pat. No. 6,013,765. As shown therein, expression of GAGE was observed in melanoma tumor tissues (e.g., Van den Eynde, p. 689, Abstract, GAGE is "expressed in a significant proportion of melanomas (24%)"). Thus, both the specification and the art support the position that GAGE is a melanoma-associated antigen.

It is noted that all of the above-described references were properly incorporated by reference into the application at paragraph [0014] of Applicants' specification. Thus, Applicants believe that the proper support is found within the specification. And there is ample support in the art that the NY-ESO-1, BAGE, and GAGE are in fact understood to be melanoma-associated antigens. It is therefore respectfully requested that these rejections be withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph (new matter)

Claims 11 and 12 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not sufficiently described in the specification. The Examiner alleged that "the specification and the status of the art do not support that a NY-ESO-1 antigen, a BAGE antigen, and a GAGE antigen" are melanoma-associated antigens. Applicants respectfully disagree.

As described in the preceding section, all of NY-ESO-1 antigen, BAGE antigen, and GAGE antigen are described in the specification and the art. All of the cited references were properly incorporated by reference into the application at paragraph [0014] of Applicants' specification. Thus, Applicants believe that the proper support is found within the specification. And, as described above, the art supports Applicants' position that the NY-ESO-1, BAGE, and GAGE are in fact understood to be melanoma-associated antigens. It is therefore respectfully requested that these rejections be withdrawn.

Rejections under 35 U.S.C. § 103(a)

A. Rejection of claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 as obvious over Paoletti (U.S. Pat. No. 5,942,235) in view of Kirkwood, et al. (J. Clin. Oncol. 19(9): 2370-80 (2001) and Aarts, et al. (Cancer Res. 62(20): 5770-7 (2002).

Claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti in view of Kirkwood and Aarts. Applicants respectfully maintain that these rejections are inapplicable to the instantly pending claims.

The instantly pending claims relate to methods for inducing an anti-tumor immune response by first administering to a subject a nucleic acid-based vaccine "as the sole active pharmaceutical agent" (e.g., alone) and subsequently administering IFNα2b "as the sole active pharmaceutical agent" (e.g., alone). This method is exemplified by Applicants' Examples 1 and 2. As described therein, patients were vaccinated with an ALVAC vector encoding a tumor antigen and then treated with high dose IFNα2b. These patients demonstrated a robust anti-tumor immune response, including the elimination of systemic metastases (e.g., patients M166 and M335). Surprisingly, and in contrast to the teachings of the cited art, this was accomplished without simultaneously administering vaccine and cytokine. It is further noted that this was accomplished without additional vaccinations subsequent to administration of cytokine (e.g., as in new claim 35). As described below, the cited art does not teach or suggest an immunization protocol that does not include simultaneous administration of vaccine and cytokine or repeated "boost" vaccinations following administration of cytokine.

Paoletti only speaks generally to the use of vectors and cytokines. As such, the Examiner points to Kirkwood as teaching a high-dose interferon treatment protocol. However, the Examiner also notes that Kirkwood does not teach combining high dose IFNα2b with a tumor antigen vaccine. To satisfy this deficiency, the Examiner references Aarts. Applicants respectfully submit that this combination of references cannot support a *prima facie* case of obviousness regarding the instantly pending claims.

Aarts does not suggest or demonstrate administration of vector alone, followed by cytokine alone, as instantly claimed. The Examiner indicated at p. 12 that Aarts teaches a "prime (i.e. initial) administration of a composition comprising a nucleic acid encoding human tumor antigen. . . followed by multiple subsequent booster vaccinations, which comprising administration of recombinant cytokines. . . ." However, Aarts' priming step is actually performed by administering vaccine and cytokine simultaneously which, as discussed below, is taught to be "essential in inducing antitumor activity". At page 5771, col. 2, first full paragraph ("Materials and Methods"), Aarts states:

> In addition to prime vaccinations, mice of indicated groups (see Table 1 and figure legends) received 20 mg of rGM-CSF s.c. at the vaccination site (once a day for 4 days), and /or 16,000 IU recombinant IL-2 i.p. (every 12 h for 4 days, designated low-dose IL-2; Ref. 14) . . . For boost

> vaccinations, vaccine vector was admixed with 10^7 pfu of rF-GM-CSF, and/or low dose IL-2 was given i.p.

All of the experiments described by Aarts involve the co-administration of vaccines and cytokines at least during the priming step. The data shown in Figs. 1 and 3 relates to animals vaccinated with CEA/TRICOM vectors and simultaneously administered GM-CSF and / or IL-2. The data of Figs. 2, 4, and 5 relates to animals to which CEA-expressing tumor cells were first administered without cytokines, which was followed by administration of a CEA/TRICOM vaccine with the simultaneous administration of GM-CSF and / or IL-2. In summarizing their results, Aarts teaches that vaccination with an expression vector encoding a tumor antigen simultaneously with cytokine(s), "without a primary vaccination. . .increased survival time" of tumor-bearing animals (p. 5777, col. 1, lines 2-5) and that:

> ...the use of cytokines, local granulocyte macrophage colony-stimulating factor (GM-CSF) and low-dose systemic interleukin 2, in combination with vaccine is essential in inducing antitumor activity, as compared with the use of cytokines alone, or the use of vaccines without cytokines. (p. 5770, Abstract)

Aarts does not suggest administering a vaccine as the sole active pharmaceutical agent, and then administering a cytokine as the sole active pharmaceutical agent, as instantly claimed. In characterizing the combination of vaccine and cytokine as "essential in inducing antitumor activity", Applicants believe that Aarts actually teaches away from the instantly claimed subject matter. The skilled artisan would not have been motivated to ignore the "essential" step of co-administering vaccine and cytokine until Applicants' disclosure was in hand. As such, Applicants do not believe Aarts is applicable to the instant claims in that the reference only teaches the simultaneous administration of vaccine and cytokine.

As suggested by the Examiner, Paoletti does not teach high dose IFNα2b therapy, and Kirkwood does not teach combining high dose IFNα2b therapy with expression of a tumor antigen. For the reasons described above, Applicants respectfully maintain that Aarts cannot satisfy the deficiencies of Paoletti and Kirkwood in rendering the instantly

pending claims obvious. As such, it is respectfully requested that these rejections be withdrawn.

B. Rejection of claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 as obvious over Paoletti (U.S. Pat. No. 5,942,235) in view of Kirkwood, et al. (J. Clin. Oncol. 19(9): 2370-80 (2001), Aarts, et al. (Cancer Res. 62(20): 5770-7 (2002), and Kawakami, et al. (U.S. Pat. No. 5,844,075).

Claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti in view of Kirkwood, Aarts, and Kawakami. Applicants respectfully maintain that these references cannot be combined to support a *prima facie* case of obviousness against the instantly pending claims.

Applicants' position with respect to the combination of Paoletti, Kirkwood and Aarts were set forth in the preceding section, and are maintained with respect to these rejections. As suggested by the Examiner, Paoletti does not teach high dose IFNα2b therapy, and Kirkwood does not teach combining high dose IFNα2b therapy with expression of a tumor antigen. Applicants do not believe Aarts is applicable in that the reference only teaches the simultaneous administration of vaccine and cytokine. Applicants respectfully maintain that Aarts cannot satisfy the deficiencies of Paoletti and Kirkwood as suggested by the Examiner. Kawakami is only cited as teaching immunogenic peptides, including those of Applicants' SEQ ID NOS.: 2 and 3. Applicants respectfully maintain that Kawakami's description of gp100 peptides cannot satisfy the deficiencies of Aarts. As such, Applicants do not believe the combination of Paoletti in view of Kirkwood, Aarts, and Kawakami render the instantly pending claims obvious. Accordingly, it is respectfully requested that these rejections be withdrawn.

CONCLUSIONS

Reconsideration of this application is respectfully requested. Applicants believe the claims are in condition for allowance and respectfully request the issuance of a Notice of Allowance as soon as possible. The Examiner is encouraged to contact the undersigned if it is believe doing so would expedite prosecution of this application.

Respectfully submitted,

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